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Changes in the Eye Fundus in Metabolic Syndrome

Radjabov Bekzod Madirim ugli, Ergashev Sukhrob Tahir ugli, Gulmanov Ilyich Dzhumabaevich
Tashkent Medical Academy

Abstract: Eye diseases such as diabetic retinopathy, central retinal artery occlusion, cataracts, age-related macular degeneration, glaucoma, and dry eye syndrome are associated with many components of metabolic syndrome. Several studies also show an association between metabolic syndrome and the retinal microvasculature. Studies have reported associations between components of metabolic syndrome and eye diseases such as dry eye syndrome. This article is devoted to the analysis of modern data and literature on fundus changes in metabolic syndrome.

Keywords: metabolic syndrome, eyes, retina, diseases.

Relevance. According to the World Health Organization (WHO), the prevalence of metabolic syndrome among the population is 20-40%, and is more common in people of middle and older age groups (50-60%) [2]. A study of the etiology and pathogenesis of retinal vein occlusions revealed that among systemic risk factors, arterial hypertension ranks first (42-62%), and metabolic syndrome was diagnosed in 37.4% of patients [1,3]. To date, it has been determined that metabolic syndrome as a combination of systemic factors increases the risk of morbidity and mortality from cardiovascular diseases, indirectly being a predictor of retinal venous occlusion [4,9]. There is also evidence that retinal vein occlusion in some cases is a harbinger of subsequent systemic thromboembolic complications [8]. In this regard, the study of the relationship between these diseases is relevant in terms of preventing their development and increasing the effectiveness of therapy.

Metabolic syndrome is a pathogenetically interrelated set of risk factors for cardiovascular diseases - excess body weight in combination with decreased sensitivity of peripheral tissues to insulin, hyperinsulinemia, impaired lipid purine metabolism and arterial hypertension (AH) [6,9].

Eye diseases such as diabetic retinopathy, central retinal artery occlusion, cataracts, age-related macular degeneration, glaucoma, and dry eye syndrome are associated with many components of metabolic syndrome. Several studies also show an association between metabolic syndrome and the retinal microvasculature. A study of atherosclerosis risk in communities found that metabolic syndrome was associated with microvascular changes in the retina.

The Australian Heart Eye Study found that metabolic syndrome was associated with narrower retinal arterioles but not wider retinal venules in individuals at high risk of coronary heart disease. Most of these studies were population-based or included patients at high risk of developing diabetes or heart disease [1].

Studies have reported associations between components of metabolic syndrome and eye diseases such as dry eye syndrome. Lacrimal function was studied in patients with metabolic syndrome. The authors found dysfunction of the lacrimal gland and the volume of tear fluid in these patients. The Schirmer test, tear breakup time, and ocular surface fluorescein staining index are the most commonly used tests in the diagnosis and follow-up of dry eye syndrome. Tear osmolarity is a valuable method for identifying dry eye syndrome [2].

Wang's study examined cross-sectional associations between metabolic syndrome and retinal vascular caliber in adults at high risk for cardiovascular disease. They reported that individuals with metabolic syndrome were more likely to have narrowing of the caliber of retinal arterioles, regardless of age, gender, smoking status, and the caliber of associated vessels. This association persisted in patients without diabetes. In contrast, in participants without CAD and without hypertension, there was no association between metabolic syndrome and retinal arteriolar caliber. Blood pressure, waist

circumference, and serum triglyceride levels were distinct components of metabolic syndrome that showed inverse associations with retinal arteriolar caliber, suggesting that the association is likely driven primarily by higher blood pressure, as well as obesity and dyslipidemia. They found no significant association between metabolic syndrome and retinal vein caliber.

Other studies, such as the ARIC, Funagata, and Handan Eye studies, have reported narrowing of retinal arteriolar caliber in association with metabolic syndrome. The magnitude of the difference in adjusted mean retinal arteriolar caliber between patients with and without metabolic syndrome was slightly larger in the cohort (4.30mm) compared with that observed in the Funagata (2.95mm) and Handan Eye Study (3.60mm). These results indicate that in patients at high risk for cardiovascular disease, narrowing of retinal arteriolar caliber is more closely associated with common metabolic syndrome than widening of retinal vein caliber. Also, a study in Japan suggests that narrowing of retinal arterioles is also associated with the occurrence of metabolic syndrome. However, some previous studies of metabolic syndrome have shown an association between metabolic syndrome and retinal arteriolar narrowing and venous dilatation, while others have identified associations with only one or the other of these vascular features. In the Funagata study, metabolic syndrome was associated with wider venous diameter, while the ARIC study demonstrated an association with focal arteriolar narrowing.

In the Multiethnic Study of Atherosclerosis, dilated veins were associated with obesity, hypertriglyceridemia, low HDL, and hyperglycemia, and constricted arterioles were associated with hypertension. Narrowing of retinal arteriolar caliber is thought to indicate changes in endothelial function associated with hypertension and aging, including intimal thickening, medial hyperplasia, hyalinization, and arteriolar sclerosis. Generalized constriction of retinal arterioles may also reflect abnormalities of vasomotor constriction affecting vascular smooth muscle cells and neuromuscular junctions. Research has previously shown that in children, obesity is associated with arteriolar narrowing, possibly due to endothelial dysfunction.

Previously, the Blue Mountains Eye Study also showed that dyslipidemia is associated with arteriolar narrowing. On the other hand, wider retinal vein caliber is widely associated with systemic inflammation and related conditions, including atherosclerosis, smoking, and hypercholesterolemia. Retinal vein dilatation also appears to be associated with biomarkers of malnutrition, particularly albumin and transthyretin [3–6].

Ocular complications reported to be associated with metabolic syndrome include retinopathy, high intraocular pressure, cataracts, macular degeneration, and exophthalmitis. The alarming increase in the prevalence of obesity or metabolic syndrome is likely to further exacerbate the risk of obesity-related ophthalmic changes. Retinal diseases, including age-related macular degeneration (AMD), retinitis pigmentosa (RP), and diabetic retinopathy (DR), represent a leading cause of irreversible blindness in developed and developing countries. While AMD is characterized by loss of central vision, RP is typically characterized by rod and cone dystrophy, resulting in loss of rod and cone photoreceptors and predominantly degeneration of rod photoreceptors. In some populations, obesity is a major component of metabolic syndrome, which is associated with microvascular changes in the retina. In addition, retinal degeneration has been reported as a component of obesity [7–10].

According to the epidemiological study Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), with a duration of type 1 diabetes (T1DM) of more than 20 years, the incidence of DR reaches almost 100% [3], with complete loss of vision in every 30th patient [4]. In general, signs of DR appear 5 years after the onset of T1DM in 20% of patients, after 10 years in 60%, and after 20–30 years in almost all. In type 2 diabetes (T2DM), 20 years after the onset of the disease, approximately 2/3 of patients have DR, while in a fifth of patients the disease is detected in the proliferative stage [5].

Diabetic macular edema (DME) is one of the main causes of vision loss in patients with diabetes, which has been established by numerous clinical studies. Patients with T2DM are at higher risk of developing macular edema. The incidence of DME increases with the severity of DR, reaching 70% in the proliferative stage of this complication [11]. According to the results of the Diabetes Control and Complications Study (DCCT-international studies), 27% of patients with T1DM develop DME within

9 years after the onset of the disease [12]. In patients with T2DM, its prevalence increases from 3% of cases with a disease duration of less than 5 years to 28% with a disease duration of 20 years or more [13].

The results of the study by Matthias Huber et al may indicate that features of metabolic syndrome are exacerbated by microvascular changes. However, they only looked at one aspect of microangiopathy in a limited area of the rat retina. Moreover, other aspects of microangiopathy, as they can be studied in humans throughout the fundus using more sophisticated methods, were not determined in the rat model studied. Taken together, these data indicate the presence of underlying microangiopathy in the retina of obese animals. As a consequence of discrete morphological damage to the retina in obese animals, we further asked whether functional deficits could be observed in this setting of microangiopathy in the absence of major structural changes in the retina [20].

The electroretinograms of obese rats were normal, indicating that the processing of light signals of varying intensities was essentially intact. Therefore, it can be concluded that obese rats retained their visual ability, indicating that neural networks and complex interactions with glial cells were not fundamentally disrupted by metabolic changes in obese animals. In this regard, the above-described morphology with intact retinal integrity correlated well with overall good ERG function. However, several individual tests, such as scotopic and photopic ERG, 30 Hz flicker ERG, may be associated with impaired bipolar or Müllerian glial cell function. Since further sensory bipolar cell activity remained unchanged on electroretinograms, Müller cells were the most likely cause of b wave reduction. Thus, Müller cells may be a critical cell type in the initial pathogenesis of early retinopathy in type 2 diabetes with metabolic syndrome. They may be responsible for the modulation of many key functions in retinopathy, as they are involved, for example, in angiogenesis [14].

In the maintenance of blood-retinal barriers, in the metabolism of neurotransmitters and in the homeostasis of retinal fluid. This suggests that Müller cell-related pathogenesis is characteristic of type 2 diabetes with obesity and metabolic syndrome, since in rats with STZ-induced diabetes, the reduction of b-waves usually occurs not before, but simultaneously with changes in the amplitudes of oscillatory potentials. However, changes in oscillatory potentials in obese animals were limited by a small but significant increase in latency. This characteristic of oscillatory potentials precedes leakage on fluorescein angiography and is therefore consistent with the mild microangiopathy found in the morphological analysis of this study. In humans, this ERG pattern is typical of diabetic patients with discrete microangiopathy, but not with more profound fundus changes such as hard exudates that represent later stages of diabetic retinopathy. In this regard, increased latency of oscillatory potentials without decreased amplitude in obese rats in combination with early microangiopathy is similar to early diabetic retinopathy in humans. The findings in obese animals are complemented by subtle photoreceptor dysfunction indicated by altered wave parameters such as decreased amplitude, increased latency, and higher wave values. Notably, altered photoreceptor function has also been described in a rat model of induced diabetes based on varying findings. In addition, disturbances in a- and b-wave parameters may be a consequence of circulatory disturbances characteristic of diabetic retinopathy, and therefore may correlate with morphologically described microangiopathy [11-13].

Recently, the influence of diabetes duration on the prevalence of diabetic retinopathy (DR) in patients with type 2 diabetes and MS, clinical, functional and metabolic relationships in coronary heart disease and DR in patients with type 2 diabetes, the role of tissue renin-angiotensin- aldosterone system in the development of MS, diabetes and its vascular complications, and even the effect of a diet containing omega-3 fatty acids on the risk of DR [18]. Although the exact pathogenesis of DR remains unclear, it is now believed that chronic inflammation, as discussed above, that occurs in type 2 diabetes in combination with obesity and other metabolic syndrome clusters, and associated processes contribute to neuronal, glial and microvascular lesions of the retina. It is generally accepted that, in addition to vascular changes, subclinical inflammation and leukostasis, structural and functional damage to nonvascular cells (ganglion cells, glial and microglial cells) contribute to the pathogenesis of DR. There is evidence that neurodegeneration of retinal neurons and glial cells occurs even before the appearance of microaneurysms. Since the key point in the formation of metabolic syndrome is insulin

resistance, induced by certain adipose tissue hormones and lipocytokines, compensatory hyperinsulinemia that occurs in obesity through IGF-1 can influence hyperplastic, proliferative, tumor processes and, possibly, the development of proliferative DR. However, the role of adipose tissue hormones and proinflammatory lipocytokines, in particular tumor necrosis factor alpha (TNF-α), which is involved in the initiation of chronic inflammation in type 2 diabetes and insulin resistance, in the development and progression of DR has not yet been fully elucidated. Previous studies have shown that ROS, signaling molecules of endothelial cell disruption, contribute to the modulation of endothelial function as well as the expression of inflammatory cytokines. In patients with diabetes, an increase in general (nonspecific) inflammatory process was observed compared with individuals without diabetes, which was manifested by an increase in serum TNF-α levels.

Schram et al. examined the association of inflammatory markers with vascular complications in diabetes and showed that there is a strong independent association between TNF-α, interleukin-6 (IL-6), C-reactive protein and DR. The profile of intraocular TNF-α and IL-6 in diabetic patients at various stages of DR demonstrates that intraocular inflammation appears to be involved in the development of proliferative DR, but is not significant in the early stages of its development. Determining the possible relationship between serum inflammatory marker levels and retinopathy showed an association between TNF-α and proliferative DR in patients with diabetes. The role of the adipokine leptin in the development and progression of DR in obesity is also the subject of active discussion. It has been shown that obesity and DR may be associated due to oxidative stress and hyperleptinemia [11, 19]. Plasma leptin levels increase in obesity and are positively correlated with visceral and subcutaneous body fat [17]. High plasma leptin levels have been found to be associated with hypertensive retinopathy and DR. Findings relevant to DR show that leptin promotes vascular endothelial cell proliferation and angiogenesis in vitro and neovascularization in vivo [12].

Some data link the participation of leptin in the occurrence of retinal pathology with its increased level in the vitreous body in proliferative DR and retinal detachment, as well as with its presence in fibrovascular epiretinal tissue [19]. The detection of leptin in the vitreous body of the eye may be a possible factor in the development of vascular and proliferative diseases of the retina. Intraocular leptin production is thought to be involved, although not critically, in the etiopathogenesis of proliferative DR, but studies indicate that the relevant source of leptin in the vitreous fluid is serum penetration there [11]. Previously observed leptin-induced stimulation of angiogenesis and neovascularization supports the possibility that it may play an important role in the development of DR before its proliferative phase [15]. It has been shown that the occurrence of the non-proliferative stage of DR is characterized by an increase in the proportion of patients with hypertension and dyslipidemia against the background of obesity. The transition to the preproliferative stage of DR is associated with a further increase in the relative frequency of dyslipidemia compared with the first stage. The development of the proliferative stage of DR occurs against the background of an increase in the relative frequency of hypertension compared to the second stage against the background of obesity, dyslipidemia and hypertriglyceridemia. With the progression of DR from the non-proliferative stage to the proliferative stage in type 2 diabetes as a component of MS, there is a significant increase in the concentration of fibrinogen in the blood [20].

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